Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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The Use of Antiretroviral Agents Not Approved for Use In Children (Last updated November 1, 2012; last reviewed November 1, 2012)

Panel's Recommendations

- Children may need to use antiretroviral (ARV) drugs that are not yet approved for their age because many of the recently approved, more convenient, and potent agents are approved for use in adults before pharmacokinetic (PK), safety, and efficacy data are available in children **(AII)**.
- Dosing in a child of ARVs only approved for adults cannot simply be inferred from a simple calculation using the adult dose and the child's weight **(AII)**. Such use of ARVs should always be done in collaboration with a pediatric HIV specialist, who may have access to unpublished data about safety and PKs of ARVs that are not yet Food and Drug Administration (FDA)-approved for children **(AI*)**.
- Whenever possible, use of ARVs that are not yet FDA-approved for children should be done in the context of clinical trials that can generate the data needed for pediatric approval **(AIII)**.

Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*

Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = expert opinion*

† Studies that include children or children and adolescents but not studies limited to postpubertal adolescents

It has long been the practice of physicians, especially pediatricians, to prescribe medications in off-label situations, meaning for indications or populations that do not fall within the official, Food and Drug Administration (FDA)-approved indication.[1] The relatively small market for pediatric antiretroviral (ARV) drugs and few children available to participate in clinical trials have delayed or prevented studies to obtain an FDA pediatric label indication for some ARV drugs at the same time their use in adults is approved. Pediatric HIV specialists may need to prescribe these agents because drugs currently available for pediatric use afford few options for heavily treated children and adolescents with high levels of resistance and because the newer agents offer improvements in tolerability and ease of adherence with less frequent dosing.

One distinct advantage of some of the newer medications is improved tolerability. Examples include a reduction in frequency or severity of side effects with newer protease inhibitors (PIs) and the ability to create simpler regimens using fixed-dose combination tablets or once-daily preparations. The incentive to use these drugs to avoid toxicities and simplify regimens is that these regimens will lead to improved adherence, and thus, better long-term outcomes.

Another major factor leading to off-label use of ARVs has been the development of new drugs belonging to novel classes of agents effective against resistant virus. In the United States, many older perinatally infected children have extensive drug resistance resulting from treatment with multiple non-suppressive regimens. Cross resistance between fully approved ARVs within a class makes it difficult to find a combination of agents likely to fully suppress the virus. In an effort to create a regimen likely to achieve complete virologic suppression in an individual patient, providers must identify at least two and preferably three drugs with demonstrated activity against the patient's virus. Success is almost impossible in heavily treatment-experienced children using only drugs with approved pediatric label indications; thus providers may use

drugs not yet approved for children in order to provide optimal virologic response.

The use of agents not yet approved for pediatric use causes some difficulties. One of the major issues is lack of data on appropriate dosing in children. Agents are approved for adult use before being approved for pediatric use because safety and pharmacokinetic (PK) studies in children have not yet been completed. Sometimes studies in children are ongoing and some data are available, but other times, pediatric studies have not yet begun. It is essential for providers prescribing agents for off-label use to consult with pediatric HIV experts to avail themselves of the latest information from ongoing studies.

The possibility of age-related side effects is another concern when initiating off-label ARV use. To date, no ARV has been found to have adverse effects that preclude use uniquely in children, but until an agent has been tested in children, it cannot be considered to be free of such an effect. In addition, adverse effects noted in adults may be of more substantial concern in a growing and developing child.

Difficulties in pediatric dosing for off-label use of ARV drugs are even more problematic than the potential for adverse effects. As absorption, hepatic metabolism, and excretion change with age, so will drug levels change in children.[2] The difficulty in dosing children as they increase in weight is exacerbated by changing PKs. In clinical trials of several ARV agents, direct extrapolation of a pediatric dose from an adult dose, based on a child's body weight or body surface area, was shown to result in an underestimation of the appropriate pediatric dose.[3]

In summary, use of ARV agents without a pediatric indication is an absolute necessity for treatment of some HIV-infected children, but such off-label use must be done with care. **It is essential that a provider consult with a pediatric HIV specialist to identify any particular concerns with each agent, to access any available data from clinical trials or other limited off-label pediatric use, and to investigate the availability of suitable clinical trials.**

References

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2. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. Sep 18 2003;349(12):1157-1167. Available at http://www.ncbi.nlm.nih.gov/pubmed/13679531.
3. Fletcher CV, Brundage RC, Fenton T, et al. Pharmacokinetics and pharmacodynamics of efavirenz and nelfinavir in HIV-infected children participating in an area-under-the-curve controlled trial. *Clin Pharmacol Ther*. Feb 2008;83(2):300-306. Available at http://www.ncbi.nlm.nih.gov/pubmed/17609682.